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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,105	10/25/2005	Takafumi Ishii	62936 (46342)	2820

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EXAMINER	
YAO, LEI	
ART UNIT	PAPER NUMBER
1642	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,105	ISHII ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,17,18,21,24,25,28,29,31,32,37-40,42,43,46 and 47* is/are pending in the application.

4a) Of the above claim(s) *1-3,10,11,14,21,24,28,29,31,32,37-40,42,46 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-9, 12-13, 17-18, 25, and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/18/2005 and 3/6/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group 1 (claims 4-10, 12, 13, 17-18, 25, 28-29, and 43) drawn to a polynucleotide in the reply filed on 11/27/2007 is acknowledged.

Applicant requests reconsideration of the restriction requirement on the ground that examination of the groups together should not impose an undue burden, which has been considered. In response, according to PCT Rule 13.2 restriction requirement for this 371 national stage application is determined by whether unity of invention exists in this application, not by whether there is search burden for the examination. The unity of invention is based on only when the shared same or corresponding technical feature is a contribution over the prior art. In this case, the inventions listed as group I drawn to a protein and group II drawn to DNA do not related to a single general invention concept (the unity of the invention) because the lack the same or corresponding special technical feature. The technical feature of group II (DNA), which is shown by GeneBank accession number T50605 of SEQ ID NO: 4 as stated in the office action dated 10/4/2007. Therefore, the invention Group II does not make a contribution over the prior art and the technical feature of the Group II is not a special technical feature for group I and II, the unity of inventions including Group I and II drawn to DNA, Protein and method of using the protein or DNA is lacking. Therefore the requirement is made Final.

Claims 15-16, 19-2, 22-23, 26-27, 30, 33-36, 41, 44-45, are 48-50 are cancelled.

Claims 1-14, 17-18, 21, 24-25, 28-29, 31-32, 37-40, 42-43, 46-47 are pending.

Claims 1-3, 10-11, 14, 21, 24, 31-32, 37-40, 42, 46-47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

Claims 28 and 29 are also withdrawn as being drawn to a nonelected species.

Claims 4-9, 12-13, 17-18, 25, and 43 drawn to polynucleotides (DNA) to the extent of SEQ ID NO: 16 are examined on the merits. It is noted that antisense polynucleotide recited in claims 17-18 are considered as complement DNA, not RNA, because antisense RNA play an inhibitory function for gene expression, which is examined separately.

Information Disclosure Statement

The information disclosure statement (s) (IDS) submitted on 2/18/2005 and 3/6/2006 are/is considered by the examiner and initialed copies/copy of the PTO-1449 are/is enclosed.

Claim Objections

1. Claim 4 and 25 are objected to for depending on the non-elected claim 1 reciting different subject matter (protein). The objection can be obviated by rewritten the claim 4 in an independent form.

2. Claim 12 and 18 are objected to because the term only "a pharmaceutical" recited in the claims. As stated in the claims, the pharmaceutical comprising the active component and salt thereof, the "pharmaceutical" comprises more than one component and should be written as "a pharmaceutical composition comprising....". Correction would be appreciated.

Specification

Specification is objected to because it contains an embedded hyperlink and/or other form of browser-executable code at paragraph 487 and 498. Applicant is required to check entire specification and delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 4-9, 12-13, 17-18, 25 and 43 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The products, polynucleotides of SEQ ID NO: 16, or a transformed comprising the polypeptides, which do not constitute patentable

subject matter as defined in 35 U.S.C. 101. The claimed inventions do not show involvement of the "hand of man". Amending the claims to require that the polynucleotides and the transformant are purified or isolated would indicate the "hand of Man".

The following is a quotation of the **first paragraph of 35 U.S.C. 112:**

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement-drawn to pharmaceutical composition comprising antisense of polynucleotide used for therapeutic purpose.

Claims 17 and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In this rejection, claims 17 and 18 are interpreted as antisense DNA or RNA complementary to the polynucleotides of SEQ ID NO: 16 having the inhibitory function and being intended use for therapeutic purpose.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir,1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to antisense polynucleotide and pharmaceutical composition comprising the antisense to the polynucleotide of SEQ ID NO: 16. The antisense DNA or RNA in

the pharmaceutical composition would be intended to be used for the therapeutic purpose to inhibit the expression of the gene product of SEQ ID NO: 16. However, the scope of the instant claims is not commensurate with the enablement of the instant disclosure because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art.

The specification on page 35 teaches that the antisense polynucleotide is generally constituted by bases of about 10 to about 40, preferably about 15 to about 30 and teaches a pharmaceutical composition comprising antisense (page 48+). The specification, examples 2, 3 and 19, teaches a in vitro method of inducting apoptosis of cells, A549 and NCI-H226, by antisense oligonuleotide transfection, and states that TACT427 protein (encoded by SEQ ID NO:16 and its homologies) is disappeared in both cell lines (page 102 line 6+). However, the problems related to therapeutic use of nucleic acids were well known in the art at the time of invention (see for example Agrawal et al. Molecular Medicine Today, 2000, vol. 6, p 72-81), Opalinska et al. (Nature Reviews Drug Discovery, 2002, vol. 1, p. 503-514) and Jen et al. (Stem Cells 2000, vol. 18, p 307-319)). Such problems include the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect.

Jen et al. state (see page 313, second column, second paragraph)

> "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Opalinska et al. state on page 511

> "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and in column 2 of the same page, "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the

> endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed pharmaceutical composition *in vivo* in all organisms, with a resultant inhibition of gene expression. The specification provides *examples as set forth above*, however, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery of the exemplified cell line would not be applicable to delivery of oligonucleotides to any organism. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism). For example, Agrawal et al. (see p 79-80, section entitled "Cellular uptake facilitators for *in vitro* studies") states

> "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....*In vitro*, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide."

Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results. Given these teachings, the skilled artisan would not know *a priori* whether introduction of broadly disclose oligonucleotides *in vivo* by commonly used methodologies of the instant invention, would result in the oligonucleotide reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful inhibition of expression of a target gene. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acids in therapeutic applications in any organism. The teachings of the prior art does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods.

Thus, while the specification is enabling for the examples set forth in the specification, the specification is not enabling for the broadly claimed antisense polynucleotide substantially

complementary to the polynucleotide of SEQ ID NO: 16 and a pharmaceutical composition for the therapeutic use as the art of inhibiting gene expression by introducing antisense oligonucleotides into an organism is neither routine nor predictable. The amount of experimentation required is such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 17 and 18 are not enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

1. Claims 4-9, 12, 13, 17, and 18 are rejected under 35 U.S.C. 102(b) or 102 (e) as being anticipated by Williams et al., (WO/1999/038972, published 5/8/1999 or its national stage US Patent, No 6964868, filing March 2000) as evidenced by DNA database search result.

Claim 4 is drawn to a polynucleotide comprising a polynucleotide encoding a protein comprising the same or substantially the same amino acid sequence of SEQ ID NO: 15 or a partial peptide thereof, wherein the polynucleotide is a DNA (claim 5),
wherein a base sequence represented by SEQ ID NO: 16 (claim 6) or consisting of a base sequence represent by SEQ ID NO: 16 (claim 7).
Claim 8 and 9 are drawn to a recombinant vector and transformant comprising the polynucleotide of claim 4.
Claims 12, 13, 25 are drawn to a pharmaceutical, diagnostic agent, a kit comprising the polynucleotide.
Claims 17-18 are drawn to an antisense complement and a pharmaceutical comprising the antisense or complement to the polynucleotide of SEQ ID NO: 16.
Claim 25 and 43 are drawn to A kit comprising the polynucleotides of SEQ ID NO: 16.

For this rejection, claims are given the broadest interpretation for the term "substantially the same", which reads on any homologous polynucleotide to the sequence of SEQ ID NO: 16,

term "a base sequence" read on a polynucleotide encoding a peptide as small as two amino acids or any length of a partial polynucleotides of SEQ ID NO: 16.

For this rejection the intended use of a pharmaceutical or diagnostic agent is given no patentable weight.

For this rejection, the antisense polynucleotide recited in claims 17-18 are interpreted as any antisense polynucleotide comprising full or partial DNA or RNA, which is complementary to the polynucleotide of SEQ ID NO: 16.

Williams et al., disclose a polynucleotide with 289 nucleotides (SEQ ID NO: 293), which is a partial sequence of the polynucleotide of SEQ ID NO: 16 with 99.3% local nucleotide identity to the polynucleotide of SERQ ID NO: 16 at position 2620-2889 as evidenced by DNA database search result (attached). The polynucleotide taught by Williams et al., would encode a polypeptide which is partial peptide of SEQ ID NO: 15 and reads on a base sequence of SEQ ID NO: 16. Williams et al., disclose a vector and a host cell that carry the nucleotides (col 7 and 10-11 and also disclose pharmaceutical composition comprising the nucleosides (col 32, 47+, US patent). Williams et al., further disclose antisense nucleotides that are complementary to the sequence of the SEQ ID NO: 16 and pharmaceutical composition comprising the antisense (col 19 and 47+ US Patent).

2. Claims 4-7 and 17 are rejected under 35 U.S.C. 102 (b) as being anticipated by GeneBank (EST) Accession No. BQ68095 submitted April, 2002 as evidenced by Database search result (page 3-4).

Claims 4-7 and 17 are set forth above.

The Accession No. BQ68095 discloses a polynucleotide having 973 nucleotides that is 100% local identity to the polynucleotide at position 1-690 of SEQ ID NO: 16 as evidenced by the search result (see attached). The polynucleotide would encode a partial peptide or substantially the same peptide of SEQ ID NO: 15. The polynucleotide also reads on a base sequence of SEQ ID NO: 16. Since the DNA contain a double strand polynucleotides, which would read on an antisense and complement to the SEQ ID NO: 16.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquires set forth in Graham V. john Deere Co., 383 U.S. 1, 148 USPQ 459 (1996), that are applied for establishing a background for determining obviousness under 25 U.S. C. 103 (a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or obviousness

Claims 25 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over being anticipated by Williams et al., (WO/1999/038972, published 5/8/1999 or its national stage US Patent, No 6964868, filing March 2000) in view of Croce et al., (US Patent, 5928884).

Claims 25 and 43 are drawn to a kit comprising a polynucleotide of SEQ ID NO: 16.

For this rejection the intended use of a kit is given no patentable weight.

The teaching of Williams et al., is set forth above.

Williams et al., does not teach a kit specifically comprising a polynucleotide of SEQ ID NO: 16.

However, formation of a kit using known component is within the purviews of one skilled in the art. For example, Croce et al., teach diagnostic kit comprising a DNA probe as an active ingredient (col 44, line 32-67).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the polynucleotide of the primary reference by Williams et al.,

comprising full or partial sequence of SEQ ID NO: 16 in a kit of the secondary reference by Croce et al., with the expected benefit for the screening a compound for the cancer therapy. One of ordinary skill in the art would have been motivated with reasonable expectation of success to use the polynucleotide of Williams et al to the kit of Croce et al., because Williams et al., have shown partial polynucleotide and Croce et al., have shown a method of making a kit.

Conclusion

No claims are allowed. The polynucleotide consisting of SEQ ID NO: 16 is free of the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao,
Examiner
Art Unit 1642

LY

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER